M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: February 8, 2000

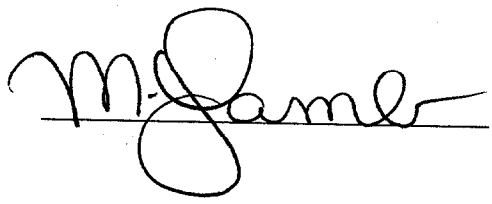
To: Dockets Management Branch (HFA-305)

From: Melissa Lamb
Office of Generic Drugs

Subject: Stability Guidance

This memorandum forwards overheads of a presentation to the Dockets Management Branch for inclusion in Docket 90S-0308. The following is information on the presentation for the Docket records:

Title of Presentation:	Stability Guidance (draft) Post-Approval Changes Stability Requirements/Comments
Presented for:	NAPM/GPIA/NPA/FDA Technical Workshop
Date Presented:	10/18/99
Presented by:	Richard B. Adams Donald Chmielewski
Number of Pages:	12



Attachment

90S-0308

M652

NAPM/GPIA/NPA/FDA Technical Workshop

Bethesda, MD
October 18, 1999

Stability Guidance (draft)
Post-Approval Changes
Stability Requirements/Comments

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CDER Stability Committee

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FDA Stability Guidance - Enhancements over the 1987 Guideline

Summary

- ICH
- ANDAs
- INDs
- Bracketing/Matrixing
- Post-approval changes not in SUPACs
- Site-Specific Stability
- Status of Revision

ICH

- Incorporates ICH Q1A, Q1B, Q1C, and Q5C by reference
- Domestic guidance consistent with international practice
- Recommendations for voluntary ICH switch
- Guidance revision will be coordinated with Q1A revision

ANDAs

- Includes specific guidance on stability for ANDAs
- Consistency between NDA and ANDA recommendations

INDs

- Deals with IND stability as a process
  - different information needed for different phases
  - consistent with current Phase 1 guidance (1995)
- Will coordinate revision with draft Phase 2/3 guidance

Bracketing/Matrixing

- Offers specific guidance/examples
- Potential reduction in cost of data generation/analysis
- Encourages use of these techniques

Post-Approval Changes not in SUPACs

- Published SUPACs will be referenced in revision
- Reprocessing
- Packaging Changes
- Stability Protocol

Site-Specific Stability

- Present in 1987 Guideline
- Consistency
  - Pre- and Post-Approval
  - NDA vs. ANDA
  - Division to Division
- Sub-committee meeting 9/22/99

9/22/99 Consensus: 2 Options

- Assumption: full ICH stability data package in initial NDA submission
- Validation Lot Release Data
  - C of A for 3 validated lots
  - Certification that process validation completed successfully with changes reflected for regulatory in process controls.
- FDA 3 tiered SSS scheme with modifications based on public comments

Status of Revision

- Guidance published 6/98
- Comment period closed 12/98; reopened 3/99; closed 6/99
- circa 3000 individual comments
- ICH text/SUPACs by reference
- Goal: finish revision by end of 1999

Stability Testing for Post-approval Changes

- Extent of stability data packages will depend on the likelihood of a change to affect a drug product's performance and the amount of experience an applicant has with a product
- 5 Levels are defined
  - Time of submission
  - Commitment

Stability Testing for Post-approval Changes

- Change in manufacturing process for the drug substance
- Change in manufacturing site
- Change in formulation of the drug product
- Addition of a new strength for the drug product
- Change in manufacturing process and/or equipment for the drug product

Stability Testing for Post-approval Changes

- Change in batch size of the drug product
- Reprocessing of a drug product
- Change in container and closure of the drug product
- Change in the stability protocol

Stability Data Packages

Stability Data Package	Stability data at Time of Submission	Stability Commitment
Type 0	None	Annual batch
Type 1	None	First(1)and annual prod. batches on long-term
Type 2	3 mo.'s accel.; available long term/1 batch	First(1)and annual prod. batches on long-term
Type 3	3 mo.'s accel.; available long term/1 batch	First(3)and annual prod. batches on long-term
Type 4	3 mo.'s accel.; available long term/3 batches	First(3)and annual prod. batches on long-term

Comments from *NAPM/GPIA/NPA*

- 9 comments specifically related to Stability Requirements for Post-Approval changes

Post Approval Changes - Stability - Comment #1

NPA Comment: Line 3005, p. 98

Guidance: "The reduced testing protocol should include a minimum of four data points, including the initial time point, and the expiry and two points in between. For example, drug products with a expiration dating period of less than 18 months should be tested at quarterly intervals...".

NPA: "recommends 0, 6, 12, 15 months for 15 month expiration date"

Comment #1: **Reduced Stability Protocol**

- Agree, after confirmation of proposed expiration date.
- For expiration dates of:
  - 12 months: 0, 6, 9, 12 (quarterly)
  - 15 months: 0, 6, 12, 15
  - 18 months: 0, 6, 12, 18 (semiannually)
  - 24 months: 0, 12, 18, 24
  - 36 months: 0, 12, 24, 36 (annually)

Post Approval Changes - Stability - Comment #2

NAPM Comment: Lines 3001-3014, p. 98

Guidance: "If justified, test frequency for all parameters may be reduced for *annual batches* based on accumulated stability data. Such a modification....should be submitted as a prior approval supplement".

NAPM: "If all requirements of paragraph are met, applicants be permitted to file reduced testing plans....in their Annual Reports."

Comment #2 Filing of Reduced Stability Testing in Annual report

- FDA believes that **any change** to the "Approved Stability Protocol" requires prior approval

Post Approval Changes - Stability - Comment #3

NAPM Comment: Line 227, p. 7

Guidance: "The first three production batches manufactured post approval, if not submitted in the original application, should be placed on accelerated and long-term stability studies....".

NAPM: "delete *post approval* and *accelerated and*"

Comment #3
Post-Approval Accelerated Stability Studies

- This section applies to new drug products. See line 778, page 24 for the corresponding requirement for ANDAs, which does not include accelerated stability data.

Post Approval Changes - Stability - Comment #4

NPA Comment: Line 1848, p. 58

Guidance: "In general, three to six months of stability data on one to three site-specific drug substance batches, depending on the availability of sufficient primary stability data from another site, should be provided at the time of application submission."

NPA: "...as long as sameness criteria is met, no additional stability data be required..."

Comment #4
Site-Specific Stability Data: Drug Substance

- Response:
  - ANDA site-specific requirements on pp. 61-62
  - important to demonstrate sameness of physical properties and impurity profile

Post Approval Changes - Stability - Comment #5

NPA Comment: Lines 1870-1876, p. 59

Guidance: "The complexity of the drug product dosage form is a critical factor in determining the number of site-specific batches for an original application. The quality and/or stability of a simple dosage form is less likely to vary due to a different manufacturing site than that of a complex dosage form. Three site-specific batches are needed for a complex dosage form to provide an independent and statistically meaningful stability profile for the product made at that site. *(cont.)*

Comment #5 Site-Specific Stability Data: Drug Product

- will accept validation of 3 batches or revised FDA 3-tiered table in lieu of stability

Post Approval Changes - Stability - Comment #5

One site-specific batch may be sufficient to verify the stability profile of a simple dosage form.

NPA: "Our recommendation is to eliminate stability requirements in a site transfer for drug products. A good case can be made for no additional stability data in a site transfer since the process at the new site....must be validated. .....Three batches for the transfer of a complex formulation....is excessive when only the site changes."

Comment #5
Site-Specific Stability Data: Drug Product Complexity

- Comments regarding complex drug products will be considered during revision
- Rationale for differentiation based upon degree of complexity being reevaluated

Post Approval Changes - Stability - Comment #6

GPIA Comment: Line 2834, p. 88

Guidance: "A packaging site change for other than solid oral dosage form drug products is considered a manufacturing site change and the data package that should be submitted for approval is indicated in Section IX.C.2."

GPIA: "Add *primary* before *packaging,* to read: a primary packaging site change...."

Comment #6
Primary vs. Secondary Packaging Site Changes

- Yes, FDA did not intend to require stability data to support changes in site for secondary packaging

Post Approval Changes - Stability - Comment #7

GPIA Comment: Line 2985, p. 97 (Table 20)

Guidance: "Changing the.....resin...."

GPIA: "Revise to define as changing the basic polymer (e.g., from one HDPE to another)."

Comment #7 Container/Closure Changes

- Guidance intended to require accelerated data for changing, e.g. manufacturer, formulation, use of regrind for C/C components for systems lacking equivalency protocols

Post Approval Changes - Stability - Comment #8

NAPM Comment: Line 2951-2955, p. 96

Guidance: "....on the nature of the reprocessing procedure, which can range from repackaging a batch when packing equipment malfunctions ....should be place on accelerated.... "

NAPM: "NAPM does not consider repackaging to be reprocessed and does not think accelerated stability testing is necessary....."

Comment #8
Repackaging=Reprocessing?

- Packaging is an integral part of the drug manufacturing process, thus repackaging (primary packaging) is considered the same as reprocessing

Post Approval Changes - Stability - Comment #9

NPA Comment: Line 2951-2955, p. 96

Guidance: "Any batch of the drug product that is reprocessed should be placed on accelerated and long-term stability studies….. "

NPA: "….if historical accelerated and long-term data on at least one reprocessed lot using the same reprocessing procedure, no additional stability data should be required."

Comment #9
Historical Stability Data: Reprocessed Batches

- Response:
  - reworks considered on a case-by-case basis
  - investigation required to identify causes for failure and plan to prevent recurrence
  - subsequent reworks represent "different" failures